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Clinical features associated with sleep disturbances in Parkinson's disease

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ABSTRACT

Objective: Sleep disturbances, such as REM sleep behavior disorder (RBD) and excessive daytime sleepiness, are more common in patients with Parkinson's disease (PD) than in the general population. Apart from that, their relation to PD seems to diverge considerably. Our aim was to explore the frequency and associated motor- and non-motor features of sleep related symptoms in PD.
Methods: One hundred and seven patients with PD, 65 men and 42 women, were included in a cross-sectional study. Excessive daytime sleepiness was examined by the Epworth sleepiness scale. Probable RBD (pRBD) was diagnosed by the validated REM sleep behavior disorder screening questionnaire. Further sleep symptoms were explored by the Parkinson's disease sleep scale. Motor- and non-motor symptoms were assessed and compared in patients with and without pRBD and excessive daytime sleepiness, respectively.
Results: pRBD was present in 38% and excessive daytime sleepiness was present in 29% of the patients. As opposed to excessive daytime sleepiness, pRBD showed no association to disease duration or severity. PD patients with pRBD reported more cognitive problems. There was a trend towards more autonomic dysfunction in patients with pRBD. Nocturia and sleep fragmentation were the most frequent general sleep problems reported by the patients.
Conclusions: Our results suggest that excessive daytime sleepiness is related to disease duration, and possibly caused by progressive neurodegeneration. pRBD seems to be a distinct feature present in only a proportion of PD patients.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that affects one percent of persons over the age of 60. The classic triad of bradykinesia, rigidity and rest tremor is the hallmark of the disease. However, a wide range of non-motor symptoms are an integrated part of PD, and may be just as troublesome for the patients [1]. Disturbed sleep is one of the most frequent problems, and is reported to affect 60–95% of patients with PD in various populations [2–4]. Sleep disturbances in PD include both daytime and nighttime problems. They can be caused by brain pathology related to PD, such as REM sleep behavior disorder and excessive daytime sleepiness [5,6]. Alternatively, they can be secondary to other PD symptoms, for instance insomnia due to depression, fragmented sleep because of motor symptoms or autonomic symptoms as nocturia. Finally, sleep problems can be related to PD medication, for example sleep attacks due to dopamine agonists or insomnia caused by selegiline [7,8].

REM sleep behavior disorder (RBD) is a parasomnia characterized by the absence of muscle atonia during REM sleep [9]. Affected persons often have vivid dreams, and the loss of atonia facilitates dream enactment, where movements reflect the dream content. In severe cases, movements can be vigorous and fighting. More commonly, minor jerks and different form of vocalization are described. RBD can be idiopathic, where affected persons show no sign of neurodegenerative disorders [10]. However, during recent years the disorder has received much attention due to the close relationship with development of PD and other synucleinopathies. Longitudinal studies have shown that more than 80% of patients with idiopathic RBD (iRBD) will eventually develop a neurodegenerative disorder [11,12]. The time interval before disease development is however variable and may reach several decades. A number of studies of associations between RBD and other clinical

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features of PD have been performed over the last years [13–17]. Many clinical features have been proposed to be associated with pRBD, but previous studies have been somewhat conflicting and many studies have included only a small number of patients. According to current criteria, polysomnography is needed to diagnose RBD [18]. Polysomnography is however available only at sleep centers, and the access is limited. The RBD Screening Questionnaire (RBDSQ) is a validated screening tool for RBD both in the general population and in PD patients [19,20].

Excessive daytime sleepiness (EDS) can be defined as the tendency to nod or fall asleep in various situations during daytime. Two polysomnography-based studies found no association with disturbed night-time sleep, which support the hypothesis of EDS representing a form of primary hypersomnia [21,22]. The frequency of EDS in PD is reported from 16 to 50% in different PD populations [23,24]. Focus was drawn to EDS after the observation of sudden sleep attacks associated with the use of non-ergot dopamine agonists [7]. However, later studies have found that other factors may play important roles in the development of EDS [21,23].

Sleep symptoms due to neurodegeneration are interesting because they can provide information about the pathogenesis and progression of the disease. Both RBD and EDS are frequent in PD patients, but have few other common features. To further clarify the association between sleep symptoms and clinical features of PD, we have examined sleep disturbances in a cross-sectional study of 107 patients. The study has a particular focus on RBD and EDS, and we have assessed the frequency and associated clinical features.

2. Methods

2.1. Study population

Patients diagnosed with PD at Drammen Hospital were invited to participate in this study at visits or by mail. Patients from two nearby private neurology practices were also invited. Exclusion criteria were dementia or need of a permanent caretaker. This was due to the study design, which is largely based on patient questionnaires. All patients were reexamined by a movement disorder specialist and diagnosed according to the UK brain bank criteria for PD. A total of 107 patients met the criteria and gave informed written consent. The study was approved by the Regional Committee for Medical and Health Research Ethics in South-East Norway.

2.2. Clinical assessment and evaluation of motor symptoms

Patients were examined in their regular on-state after taking their usual medication. The examination included a structured clinical interview and a standard assessment of motor function. Bed partners were encouraged to help the patient filling out the questionnaires. Use of dopaminergic and other medication was registered. Total dopaminergic medication was calculated as levodopa equivalent daily dose (LEDD) [25]. Disease severity was measured by Hoehn and Yahr stage.

All patients were evaluated by the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) that consists of four parts [26]. Part I assesses cognitive and mental symptoms by one question for each of the following items: cognition, hallucinations, depression, anxiety, apathy and impulse control problems. Part II is a patient questionnaire. The first seven questions deal with non-motor symptoms (insomnia, daytime sleepiness, pain, urgency, constipation, hypotension and fatigue). The next 13 questions examine experiences of daily living. Motor function is assessed by an examiner in part III. Motor fluctuations are evaluated through MDS-UPDRS part IV. All items are scored from zero (no problems) to four (severe problems).

Tremor score was calculated by adding the scores of self-reported tremor (MDS-UPDRS II-10) and the scores of postural, kinetic and resting tremor by examination as well as duration of resting tremor (MDS-UPDRS III 15–18). In addition, we evaluated the percentage of the total MDS-UPDRS III score accounted for by the tremor scores (MDS-UPDRS III 15–18). Postural instability and gait difficulty (PIGD) score was determined by adding self-reported scores of gait and balance (MDS-UPDRS II-12) and freezing (MDS-UPDRS II-13) and examiner evaluated gait, freezing and postural stability (MDS-UPDRS III 10–12).

2.3. Description of questionnaires

SCOPA-AUT was used to evaluate autonomic symptoms [27]. This is a patient questionnaire developed for PD patients. It includes 26 items regarding six domains: gastrointestinal symptoms, bladder symptoms, orthostatic hypotension, thermoregulation, pupillomotor function and sexuality. All items are scored from zero (never) to three (often). Extensive information on sleep related symptoms were obtained using several questionnaires. Parkinson disease sleep scale (PDSS) is a 15 item visual analog scale concerning most nighttime sleep domains. Each item are scored 0–10, where 0 represents "always" and 10 represents "never" [28]. Lower PDSS scores reflect more severe symptoms. Epworth sleepiness scale (ESS) assesses daytime sleepiness by eight questions which are scored zero (never) to three (severe) [29]. EDS was defined as a score >10 on ESS. To screen for anxiety and depression, we used Hospital Anxiety and Depression (HAD) scale which contains seven items for depression and seven for anxiety [30]. Each item can be scored from zero (best) to three (worst).

2.4. Assessment of probable RBD

We have used the RBD screening questionnaire (RBDSQ) that consists of 13 yes/no questions that assess dreams, movements and vocalization during sleep. In a previous study of PD patients 6 "yes" – answers was found to be the best cut off for detecting probable RBD (pRBD) in PD, with a sensitivity of 84% and a specificity of 96% [20]. Therefore, we have diagnosed pRBD in patients with a score of 6 and above on the RBDSQ. Both the sensitivity and specificity of the questionnaire in the PD group are comparable to the results of other screening questionnaires [31–33].

2.5. Statistical analysis

Descriptive statistics were calculated for baseline demographic and clinical data. Patients with pRBD according to RBDSQ and patients with EDS according to ESS were compared to patients without these symptoms on the following variables: Age, sex, disease duration, dopaminergic medication, Hoehn and Yahr stage, MDS-UPDRS total and sub scores, and scores on SCOPA-AUT, ESS, PDSS, RBDSQ and HAD scales. Two-group comparisons of continuous and ordinal variables were performed by the Mann–Whitney *U*-test. Categorical variables were compared using the χ^2-test. The possible associations of various demographic, disease and treatment related factors with sleep symptoms were first explored using Mann–Whitney *U*-tests. We then performed multiple linear regression analyses of those factors that independently seemed to be associated with excessive daytime sleepiness. The correlations of disease duration, Hoehn and Yahr stage, total levodopa dose, LEDD, MDS-UPDRS I, II, III and IV scores, SCOPA-AUT and HAD depression with total ESS score was explored. Variables with modest correlation (<0.3) were discarded from further analysis.

Table 1
Demographic data.

	Total ($n=107$)	pRBD ($n=41$)	No RBD ($n=66$)	p-value	EDS ($n=31$)	No EDS ($n=76$)	p-value
Sex (m:f)	65:42	28:13	37:28	0.21	23:08	42:34	0.07
Age (y)	68.2 (8.4)	69. 7 (7.7)	67.3 (8.7)	0.13	68.4 (9.0)	68.1 (8.1)	0.92
Duration (y)	4 (1–23)	4 (1–19)	3.5 (1–23)	0.59	6 (1–15)	3 (1–23)	0.03
Hoehn and Yahr	2.0 (1–4)	2.0 (1–4)	2.0 (1–4)	0.85	2.5 (1.5–4)	1.5 (1–4)	<0.01
LEDD (mg)	599 (362)	678 (365)	550 (354)	0.08	756 (419)	535 (317)	0.01
Agonist (mg/d)	162 (137)	142 (136)	174 (139)	0.24	151 (134)	151 (13)	0.13
L-dopa (mg/d)	331 (281)	419 (295)	277 (260)	0.01	442 (292)	286 (265)	0.01
MAO-B (mg/d)	60 (49)	50 (50)	66 (47)	0.11	55 (51)	62 (48)	0.51

Demographic data for the total study population and subgroups presented as mean (standard deviation) except for disease duration and Hoehn and Yahr stage presented as median (minimum–maximum). *P*-values refer to the difference between pRBD and no RBD and EDS and no EDS, respectively. Dopamine agonist use and MAO-B-inhibitor dose are calculated as levodopa equivalent daily dose. LEDD is adjusted for use of COMT- inhibitors, while levodopa dose is not. Abbreviations: RBD, REM sleep behavior disorder; pRBD, probable RBD; EDS, excessive daytime sleepiness; LEDD, levodopa equivalent daily dose; MAO-B, MAO-B-inhibitor; mg, milligrams; d, day; y, year.

The regression analysis was then run with total ESS score as the dependent variable and Hoehn and Yahr stage, MDS-UPDRS I, II and IV as independent variables. The results from multiple regression was confirmed by binary logistic regression of EDS (ESS > 10) as dependent variable and the above mentioned variables as independent variables. Statistical analyses were performed using SPSS version 18. All statistical tests were two-sided and not adjusted for multiple testing. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

One hundred and seven patients, 65 men and 42 women, completed the study. Demographic data are presented in Table 1. Disease duration varied from one to 23 years. Due to the inclusion criteria, the majority of patients had mild to moderate disease, as reflected in the median Hoehn and Yahr stage of 2.0 (Table 1). There were no difference between men and women regarding age, disease duration or Hoehn and Yahr stage. LEDD and use of agonists and levodopa were similar in men and women. Two patients were drug naïve, while three patients only used selegiline. MAO-B inhibitors in combination with other medication were used by 62 patients, while 52 patients (49%) used a combination of agonist and levodopa. Fifty patients used either agonist or levodopa alone or in combination with a MAO-B-inhibitor. We analysed each group of dopaminergic medication separately, and there were no significant differences between groups. We also assessed the use of other medication that can affect sleep. No patients used tricyclic antidepressants. Other antidepressants were used by eight patients (7%). Four patients used benzodiazepams at daytime, four patients used clonazepam at night, all due to RBD symptoms. Six patients [6%] used zopiclone.

3.2. Excessive daytime sleepiness

EDS defined as >10 points on the ESS was present in 29% of the patients (31/107). In a two group comparison, EDS was significantly associated to several variables related to more severe disease (Table 1 and Fig. 1b). In addition, EDS was associated to several motor and non-motor symptoms (Table 2). Regarding subscores of MDS-UPDRS part 1, EDS was associated with depression (mean 0.65 vs 0.39, median score 0 in both groups, $p = 0.041$), cognition (mean 0.58 vs 0.87, median score 0 vs 1, $p = 0.036$) and fatigue (mean 1.29 vs 0.72, median score 1 in both groups, $p = 0.005$), but not anxiety, apathy or hallucinations. We also found an association with LEDD, which was due to higher usage of levodopa, not dopamine agonist. There was no association with other medication. In a multiple regression analysis, MDS-

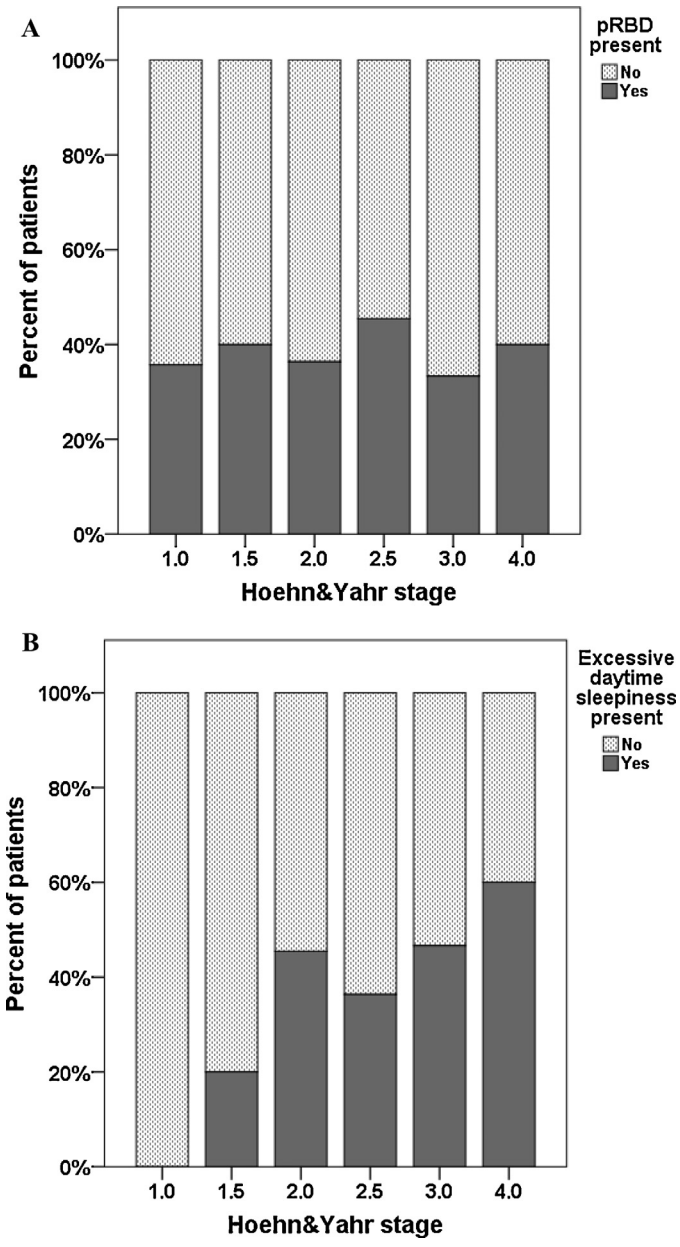

Fig. 1. Distribution of Hoehn and Yahr stage in patients with pRBD and EDS. Columns show percentage of patients with and without pRBD (a) and EDS (b) for each Hoehn and Yahr stage. Abbreviations: pRBD, probable REM sleep behavior disorder; EDS, excessive daytime sleepiness.

Table 2
Motor and non-motor features associated with pRBD and EDS.

	Total (n = 107)	pRBD (n = 41)	No RBD (n = 66)	p- value	EDS (n = 31)	No EDS (n = 76)	p- value
MDS-UPDRS I	10.5 (5.5)	11.2 (6.0)	10.2 (5.2)	0.5	14.0 (5.3)	9.1 (5.0)	<0.01
MDS-UPDRS II	12.4 (8.1)	14.2 (8.8)	11.3 (7.5)	0.1	18.0 (8.0)	10.1 (7.0)	<0.01
MDS-UPDRS III	25.5 (12.0)	26.5 (13.7)	24.8 (10.8)	0.7	30.1 (14.0)	23.6 (10.6)	0.03
MDS-UPDRS IV	1.8 (3.0)	2.1 (3.2)	1.6 (2.8)	0.7	3.7 (3.8)	1.0 (2.1)	<0.01
Tremor score	5.1 (4.0)	4.6 (3.8)	5.5 (4.2)	0.3	4.9 (4.5)	5.2 (3.9)	0.6
PIGD score	4.5 (3.0)	4.9 (3.2)	4.2 (2.9)	0.2	5.7 (3.6)	4.0 (2.6)	0.02
Tremor prop.	13 (11)	11 (11)	14 (12)	0.1	9 (10)	14 (12)	0.04
SCOPA-AUT	14.3 (7.3)	16.0 (8.0)	13.3 (6.6)	0.1	17.3 (7.2)	13.1 (7.0)	<0.01
HAD A	4.7 (3.5)	4.4 (3.6)	4.8 (3.4)	0.6	4.8 (3.4)	4.6 (3.5)	0.6
HAD D	4.2 (2.8)	4.0 (2.9)	4.3 (2.7)	0.4	5.3 (3.1)	3.7 (2.5)	0.01
RBDSQ	5.5 (3.5)	9.4 (2.2)	3.1 (1.3)	<0.01	5.4 (3.5)	5.5 (3.5)	0.8
ESS	8.3 (4.7)	8.4 (4.6)	8.3 (4.8)	0.9	14.4 (2.8)	5.8 (2.5)	<0.01
PDSS	101 (23)	95 (28)	105 (19)	0.04	92 (23)	105 (22)	0.01

Various motor and non-motor features of PD in patients with and without pRBD and EDS. Values are presented as mean (standard deviation), except for tremor proportion, which is presented as percentage. *P*-values refer to the difference between pRBD and no RBD and EDS and no EDS, respectively. Abbreviations: RBD, REM sleep behavior disorder; pRBD, probable RBD; EDS, excessive daytime sleepiness; PIGD, postural instability and gait difficulty; SCOPA-AUT, Scales for outcomes in Parkinson's disease, autonomic; HAD A, hospital anxiety and depression scale, anxiety; HAD D, hospital anxiety and depression scale, depression; RBDSQ, REM sleep behavior disorder screening questionnaire; ESS, Epworth sleepiness scale; PDSS, Parkinson's disease sleep scale.

UPDRS IV was the strongest predictor of ESS, $p = 0.003$, while the impact of other variables was borderline. The regression model R^2 value was 0.26.

3.3. REM sleep behavior disorder

By using the above listed criteria, we found pRBD in 38% (41/107) of the patients. There was no difference between patients with and without pRBD regarding age, gender or Hoehn & Yahr stage (Table 1 and Fig. 1a). We found no association between pRBD and disease duration (Fig. 2). Significantly more patients in the pRBD group used levodopa (83% vs 65%, $p = 0.047$). There was no difference in agonist use or other PD medication (Table 1). There was no association with use of antidepressants or other medication.

PD patients with pRBD reported more cognitive dysfunction on MDS-UPDRS I-1 (mean 0.83 vs 0.56, median score 1 vs 0, $p = 0.047$). They also had higher mean score for fatigue (mean 1.2 vs 0.7, median score 1 in both groups, $p = 0.014$). There was no difference in other items of MDS-UPDRS 1 or MDS-UPDRS total scores (Table 2). Though only significant in one domain (thermoregulation), there is a trend towards more autonomic symptoms in PD patients with pRBD, present in all SCOPA-AUT domains (Fig. 3). There was no association between pRBD and EDS (11/41 in the pRBD-group had EDS, versus 20/66 in the non-RBD group, $p = 0.07$). Motor features such as tremor, gait, freezing and postural instability were equally distributed across groups. We found no association between pRBD and anxiety or depression. Details are displayed in Table 2. PD patients with pRBD had higher total score on PDSS (Table 2), and significantly higher scores on five of 15 items on the scale (Table 3).

3.4. General sleep problems

Nocturia and fragmented sleep were the most frequent nighttime symptoms according to the PDSS scores. Both items had a mean score at the lower end of the scale. PDSS total scores differed significantly between PD patients with and without pRBD and EDS, respectively. This reflects different scoring patterns on PDSS items addressing symptoms related to either pRBD or EDS (Table 3). PDSS total score was significantly correlated to disease duration ($p = 0.003$). The association with Hoehn and Yahr score was borderline ($p = 0.051$). There was no correlation between PDSS total score and age or gender.

4. Discussion

Our results show that both EDS and pRBD are common in a population with mild to moderate PD. Except for the high frequency, there are however few similarities between these two sleep disorders. According to our data, EDS seems to be related to more severe disease. PD patients with pRBD might however have a somewhat different underlying pathology than PD patients without RBD.

4.1. Excessive daytime sleepiness

We find that EDS is associated with depression according to HAD D, as well as the depression section of MDS-UPDRS. This supports earlier data [6]. In addition, we find that fatigue and cognition are associated with EDS. The relationship between depression, sleep and fatigue is complex, and symptoms may overlap. Although earlier studies have shown an association with reduced cognition and a correlation between fatigue and

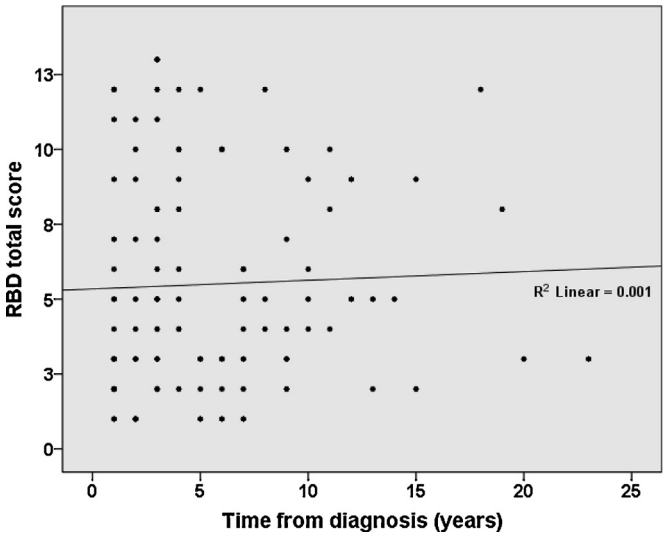

Fig. 2. pRBD symptoms versus disease duration. Scatter plot of scores on REM sleep behavior disorder screening questionnaire (RBDSQ) versus disease duration. RBDSQ can be scored from 0 to 13; minimum score for Parkinson's disease patients is 1. There is no correlation between scores on RBDSQ and disease duration, $p = 0.7$.

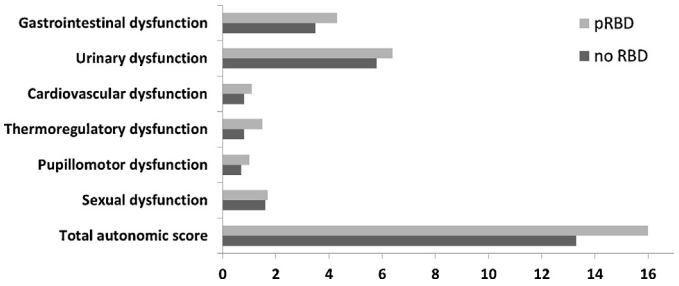

Fig. 3. SCOPA-AUT subscores in patients with and without pRBD. Comparison of SCOPA-AUT subscores for patients with and without probable REM sleep behavior disorder. The trend is towards more symptoms for the pRBD group in all domain, but the difference is significant only for the domain "thermoregulation" ($p = 0.01$). Abbreviations: pRBD; probable REM sleep behavior disorder.

depression, both fatigue and cognitive reduction are associated with higher Hoehn and Yahr stages reflecting increased disease severity [34–36]. In the multiple regression analysis, these factors did not reach significance and are probably reflecting the more advanced disease in the EDS group.

We find a significant correlation between total ESS score and motor fluctuations assessed by MDS-UPDRS IV. Motor fluctuations are an indication of increasing disease severity, and several earlier studies have shown that the presence of EDS is associated to factors reflecting disease progression. [6,23,37]. Additionally, PD patients with EDS have more advanced disease measured by Hoehn and Yahr stage and longer disease duration. These factors probably accounts for higher doses of levodopa seen in the EDS group. In the multiple regression analysis, medication is not a significant contributor, which supports this assumption

The clinical features and PSG findings of EDS in PD patients have many similarities to those of narcoleptic patients [22]. However, while loss of hypocretin is a biomarker for narcolepsy, several studies have failed to show a reduction of hypocretin by lumbar CSF measurements in PD patients [38]. On the other hand, in narcoleptics, loss of hypocretin is typically linked to cataplexy, which has never been reported in PD patients. Two studies have found a reduction of hypocretin producing cells in PD patients, correlated with disease progression rather than age [39,40]. This is in accordance with our results on EDS and disease progression. It also supports the hypothesis that susceptibility to EDS may reflect the extent of the neurodegenerative process [41].

4.2. Probable REM sleep behavior disorder

We find a frequency of pRBD in PD of 38%, which is in accordance with what other groups have found. The lack of polysomnography to confirm RBD may lead to an overestimation of pRBD because other sleep related symptoms such as sleep walking, severe periodic leg movements during sleep, sleep apnea and sleep related epileptic seizures could be misdiagnosed by the RBDSQ. On the other hand, RBD might be missed since minor symptoms may pass unrecognized by the patient or bed partner. Several recent publications on RBD are based on questionnaires, and recently a screening tool based on a single question screen was validated [31,42,43]. The sensitivity and specificity of RBDSQ in PD patients is comparable to other questionnaires and higher in the PD group compared to a group of patients with unselected sleep symptoms [19,20].

We and others have previously reported that the frequency of pRBD in PD is similar in both genders [14,20,44]. There was no association between pRBD and disease duration or disease severity, compatible with the fact that RBD is often present before motor symptoms [14,15,45]. A criticism of several earlier studies has been the lack of polysomnography confirmed RBD-diagnosis and a small number of patients. Recently, two large polysomnography based studies have however shown diverging results on demographic data such as gender and disease duration. A German study of 450 PD patients found an association between RBD, disease duration and more advanced disease measured by Hoehn and Yahr stage, but no gender difference [46]. Another recently published study including 98 patients found a male predominance in PD patients with RBD, but no difference in disease severity or duration [47].

We find an association between the presence of pRBD and levodopa dose. Previous studies have shown diverging results on this aspect. Most studies find no association, while some studies show a higher dose of levodopa or LEDD in PD patients with RBD or pRBD [13–15,46,48,49]. The results are however not directly comparable, since the methods used to calculate medication differ. If there is a true difference, it is towards higher medication use in the RBD group. Whether levodopa treatment facilitates symptoms of RBD is uncertain. There are however many indications of a more aggressive disease progression in PD patients with RBD, such as higher risk of dementia, hallucinations and more autonomic symptoms [15,50]. Higher levodopa use or LEDD in PD patients with pRBD even with comparable UPDRS III scores to PD patients without RBD could possibly indicate that patients with pRBD have

Table 3
PDSS scores.

	Total ($n = 107$)	pRBD ($n = 41$)	No RBD ($n = 66$)	p-value	EDS ($n = 31$)	No EDS ($n = 76$)	p-value
Overall sleep quality	5.7 (2.9)	5.9 (3.1)	5.6 (2.8)	0.6	5.5 (2.9)	5.8 (2.9)	0.6
Difficulty falling asleep	7.4 (2.6)	7.5 (2.5)	7.4 (2.7)	1.0	7.6 (2.4)	7.4 (2.7)	1.0
Difficulty staying asleep	4.7(3.2)	4.3 (3.3)	4.9 (3.1)	0.4	4.0 (3.1)	4.9 (3.2)	0.2
Restless legs	6.5 (3.0)	5.5 (3.3)	7.1 (2.6)	0.03	5.7 (3.1)	6.8 (2.9)	0.1
Fidget in bed	6.5 (2.8)	5.5 (3.2)	7.0 (2.4]	0.03	6.4 (2.8)	6.5 (2.8)	0.8
Distressing dreams	7.4 (2.4)	6.1 (2.7)	8.2 (1.7)	<0.01	7.2 (2.6)	7.5 (2.3)	0.6
Hallucinations at night	8.1 (2.2)	7.4 (2.7)	8.6 (1.6)	0.01	7.4 (2.8)	8.4 (1.8)	0.02
Nocturia	3.3 (3.1)	3.2 (3.3)	3.3 (3.0)	0.5	2.5 (2.5)	3.6 (3.3)	0.1
Incontinence due to "off"	8.3 (2.3]	8.2 (2.4)	8.5 (2.1)	0.7	7.1 (3.1)	8.9 (1.5)	<0.01
Numbness or tingling	7.5 (2.8)	6.8 (3.2)	7.9 (2.4)	0.1	7.5 (2.4)	7.5 (2.9)	0.4
Muscle cramps	7.4 (2.5)	7.0 (3.0)	7.7 (2.1)	0.4	6.4 (2.9)	7.8 (2.2)	0.02
Painful posturing of limbs	7.7 (2.5)	7.0 (3.0)	8.2 (2.0)	0.04	7.2 (2.8)	7.9 (2.3)	0.2
Tremor on waking	7.4 (2.5)	7.3 (3.0)	7.5 (2.2)	0.6	7.6 (2.3)	7.4 (2.7)	1.0
Tired in the morning	6.0 (2.9)	5.8 (3.3)	6.1 (2.6)	1.0	4.9 (3.1)	6.4 (2.7)	0.03
Daytime sleep attacks	7.1 (3.0)	6.8 (3.3)	7.3 (2.9)	0.5	5.1 (3.3)	7.9 (2.5)	<0.01

Scores on individual items of Parkinson's disease sleep scale presented as mean (standard deviation). Lower PDSS scores reflect more severe symptoms. *P*-values refer to differences between PD patients with and without pRBD and EDS, respectively. Abbreviations: PDSS, Parkinson's disease sleep scale.

a more severe type of PD, with effect of dopaminergic medication on motor symptoms.

There is growing evidence for an association between RBD, autonomic dysfunction and development of dementia [15,50–53]. Our study was not designed to assess cognitive or psychiatric symptoms in detail. There was however differences between PD patients with and without pRBD in MDS-UPDRS I-1, which assesses cognitive decline. Concerning autonomic symptoms, we find a tendency towards more frequent and severe symptoms in all domains in the pRBD group, but the difference is only statistically significant for one domain (thermoregulation). Earlier studies have shown an association between RBD and autonomic dysfunction, both in patients with iRBD and in PD patients with RBD [15,47,53–55]. In these studies, objective measurements of orthostatic hypotension and cardiac function have been conducted. It is possible that objective measurements are more sensitive, uncovering subclinical signs that are not reported in a questionnaire of subjective symptoms.

In our material, PD patients with pRBD have more severe sleep disturbances measured by PDSS. This difference is due to more pronounced symptoms in domains evaluating restlessness in extremities, fidgeting in bed, distressing dreams and distressing hallucinations at night. These are all symptoms that could be due to the presence of RBD. There was no difference in the eight other items, supporting the assumption that RBD is not linked to other sleep disorders.

Development of RBD is most probably associated with pathology in the brainstem region, particularly the nucleus subcoeruleus [5]. EDS is less understood, but may be related to changes in the sleep/wake regulation in the upper brainstem. It has several clinical and polysomnographic features in common with narcolepsy, and neurodegeneration in the hypothalamus is a potential explanation, though still strictly hypothetical.

4.3. Strengths and weaknesses of study

We have a relatively large number of participants compared to most other studies of RBD in PD, Nevertheless, the sample size is moderate and therefore some of the reported associations could be spurious and needs confirmation in future studies. The patients are included from the regional neurological outpatient clinics and not referred to a specialized movement disorder clinic. We have used several validated and recommended questionnaires highlighting a broad spectrum of sleep disturbances, autonomic features and other non-motor symptoms common in PD [56–58]. All patients are examined and interviewed by the same investigator.

Our results are based on self-reported problems, and the study assesses clinically relevant symptoms. A weakness is the lack of polysomnography to confirm the pRBD diagnosis. In addition, objective measurements of cognitive and autonomic function would probably have been more sensitive and might have detected subclinical symptoms. Thus, our conclusions based on self-reporting questionnaires needs to be confirmed by objective measurements of sleep and autonomic function. Another limitation of our study is the lack of follow up data. While several cross-sectional studies reporting worse symptoms in PD patients with RBD have been published, longitudinal data are scarce, elucidating the need for further studies in this field [59].

Conclusions

In our study EDS was associated with longer disease duration and higher severity of disease, and EDS therefore seems to be related to progressive neurodegeneration in PD. On the other hand, pRBD was not related to measures of disease severity, and RBD could be a specific feature present in only a proportion of PD patients.

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